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Impact of KIT mutation on efficacy of venetoclax and hypomethylating agents in newly diagnosed acute myeloid leukemia

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Abstract

Background The combination of venetoclax (VEN) with hypomethylating agents (HMAs) has emerged as a new standard treatment for older or unfit patients with acute myeloid leukemia (AML). However, the predictive factors for VEN/HMA efficacy remain unclear. In our study, we performed the first analysis of the impact of KIT mutations on therapeutic outcomes in newly diagnosed AML patients undergoing VEN/HMA regimens.

Methods In this retrospective study, we included 16 KIT-mutant AML patients receiving VEN/HMA (Cohort A), 141 KIT-wild-type AML patients receiving VEN/HMA (Cohort B), and 69 KIT-mutant AML patients receiving intensive chemotherapy (IC) (Cohort C). We compared the differences in therapeutic efficacy among the different cohorts. Furthermore, we conducted multivariate analyses in patients receiving VEN/HMA to identify factors influencing therapeutic outcomes.

Results Compared to Cohort B, Cohort A exhibited significantly lower overall response rate (ORR) (18.8% vs. 72.3%, $p < 0.001$) and measurable residual disease (MRD) negativity rate (18.8% vs. 68.1%, $p < 0.001$), with a shorter median event-free survival (EFS) (1.9 months vs. 7.8 months, $p < 0.001$). No significant difference in overall survival (OS) was observed. Among KIT-mutant patients, IC showed superior ORR (78.3% vs. 18.8%, $p < 0.001$), MRD negativity rate (75.4% vs. 18.8%, $p < 0.001$), and EFS (12.2 months vs. 1.9 months, $p < 0.001$) compared to VEN/HMA. No significant difference in OS was observed between the two cohorts. Multivariate analysis confirmed KIT mutations as an independent predictor of lower ORR (OR 0.020, 95% CI 0.002–0.211, $p = 0.001$) and shorter EFS (HR 6.318, 95% CI 2.659–15.012, $p < 0.001$).

Conclusions Our findings suggest that KIT mutations are associated with poor response and shorter EFS in AML patients treated with VEN/HMA, highlighting the importance of KIT mutation status in risk stratification and treatment selection.

Keywords Acute myeloid leukemia, KIT, Venetoclax, Hypomethylating agents, Chemotherapy, Prognosis

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Introduction

The combination of venetoclax (VEN) with hypomethylating agents (HMAs) demonstrates favorable efficacy in acute myeloid leukemia (AML) patients, achieving remission rates of approximately 70%, and has been adopted as a new standard for older or unfit patients [1–4]. However, the prediction model for VEN/HMA efficacy in AML remains unclear. Recent studies suggested that IDH1/2 mutations and NPM1 mutations may predict better outcomes, while TP53 mutations and FLT3-ITD mutations may predict poorer outcomes in patients with VEN/HMA therapy [5–7]. In addition to genetic features, tumor cell differentiation may also affect the prognosis of VEN/HMA therapy [8, 9]. Furthermore, there is another question related to which patients benefit from intensive chemotherapy (IC) and which patients benefit from VEN/HMA?

KIT mutations have been found in approximately 4–6% of newly diagnosed adult AML and 20–40% of core binding factor (CBF)-AML [10–13]. It has been reported that KIT mutations are generally associated with a poor prognosis in CBF-AML receipting IC [14–17]. However, perhaps because of the relatively low prevalence of KIT mutations and the historical reliance on chemotherapy-based induction regimens in this patient population, there have been no reports on the impact of KIT mutations on the therapeutic efficacy of patients receiving VEN/HMA treatment at present. Since 2019, China has been profoundly impacted by the COVID-19 pandemic. To mitigate the potentially fatal effects of COVID-19, a significant number of "fit" AML patients have opted for the VEN/HMA regimen. This trend has enabled the accumulation of expanded clinical data regarding KIT-mutant patients undergoing VEN/HMA therapy. Here, we performed a retrospective study to analyze the impact of KIT mutation on the efficacy of VEN/HMA treatment in newly diagnosed AML and compare the outcomes of VEN/HMA and IC in patients with KIT mutations.

Methods

Patients

We retrospectively analyzed data from newly diagnosed adult (≥ 18 yeas) AML patients at Ningbo Medical Center Lihuili Hospital and the First Affiliated Hospital of Zhejiang University School of Medicine between January 2020 and December 2023. Patients were divided into three cohorts based on the presence of KIT mutations and first-line treatment regimens: KIT-mutant AML receiving first-line VEN/HMA treatment (Cohort A), KIT-wild-type AML receiving first-line VEN/HMA treatment (Cohort B), and KIT-mutant AML receiving first-line IC treatment (Cohort C). Each course of venetoclax should be administered for at least 7 days. The HMAs used in the protocol include azacitidine and decitabine. IC includes regimens such as cytarabine + daunorubicin/idarubicin, cytarabine + homoharringtonine ± aclarubicin, and clarithromycin-based regimens. Patients received at least one course of treatment. Patients were excluded if they had (a) acute promyelocytic leukemia; (b) previously received venetoclax treatment; (c) had incomplete basic data; or (d) were lost to follow-up and unable to assess treatment response.

Baseline data

The genetic mutation data were obtained at diagnosis through targeted sequencing of a 78-gene panel using next-generation sequencing, with a detection sensitivity of 0.01%. Additional genetic data, including fusion genes (e.g., AML1/ETO fusion, CBFβ-MYH11, etc.) and chromosomal karyotypes, were obtained from all patients, enabling risk stratification according to the European LeukemiaNet (ELN) 2022 risk groups [18].

The following baseline clinical features were collected from patients: gender, age, Eastern Cooperative Oncology Group Performance Status (ECOG PS) score, types of hypomethylating agents (e.g., azacitidine or decitabine) in patients receiving VEN/HMA therapy, bone marrow blast percentage at diagnosis, French, American, and English (FAB) category [19], presence of secondary AML and allogeneic hematopoietic stem cell transplantation (allo-HSCT) in the following treatment. Significant differences in baseline characteristics were analyzed between Cohort A and Cohort B, and between Cohort A and Cohort C.

Response evaluation and endpoints

According to the ELN 2022 guidelines [18], response evaluations included complete remission (CR), complete remission with incomplete hematologic recovery (CRi), morphologic leukemia-free state (MLFS) and measurable residual disease (MRD) negativity. MRD was evaluated by multiparameter flow cytometry using bone marrow aspirate samples, with a sensitivity reaching the 0.1% level, and MRD negativity was defined as < 0.1% of aberrant blasts. The overall response rate (ORR) encompassed CR, CRi, and MLFS. Event-free survival (EFS) was defined as the time from treatment initiation until the occurrence of refractory disease, disease progression, or death from any cause. Overall Survival (OS) refers to the duration from the start of treatment to death due to any cause.

Statistical analysis

Categorical variables were presented as absolute counts and percentages. Comparison of baseline characteristics, response rates, MRD negativity rates, and early mortality rates was analyzed using the Chi-square test or Fisher's exact probability test based on sample size and expected frequencies. EFS and OS were evaluated using the Kaplan–Meier method, with between-group differences assessed by the log-rank test. A propensity score matching (PSM) method [20] with a 1:1 matching ratio via nearest neighbor and a caliper width of 0.1 was conducted to adjust the differences between cohorts. Multivariate logistic regression analyses were conducted to assess the predictive factors for response. Cox regression analyses were conducted to assess the risk factors for EFS. The 95% confidence intervals (CIs) were used to estimate odds ratios (ORs) and hazard ratios (HRs). Statistical significance was defined as $p \leq 0.05$. The impact of allo-HSCT as time-dependent covariates on EFS and OS was analyzed using Simon–Makuch plots and the Mantel–Byar test, and the statistical analyses were performed with R 4.1.1 software. All other analyses were conducted in SPSS v.25 1, and figures were generated using GraphPad Prism 9.5.1.

Results

Patient characteristics

The flowchart of patient selection is shown in Fig. 1. Finally, we included 16 patients with KIT-mutant newly diagnosed AML patients receiving first-line VEN/HMA treatment (Cohort A), 141 patients with KIT-wild-type newly diagnosed AML receiving first-line VEN/HMA treatment (Cohort B), and 69 patients with KIT-mutant newly diagnosed AML receiving first-line IC (Cohort C). The baseline characteristics of the patients are listed in Table 1. KIT-mutant patients in this study harbored KIT mutations involving exon 8, exon 10, exon 11 and exon 17, including T417, Y418, V530I, V559, D816 V, D816Y, D816 F, D816H, and N822 K. All these mutations are prognosis-associated mutations in AML. Compared with Cohort A, Cohort B had poorer performance status ($p = 0.015$), fewer patients categorized as ELN favorable-risk ($p < 0.001$), and lower proportion of CBF-AML cases. Other baseline features were comparable between Cohorts A and B. Compared with Group A, patients in Group C were younger in age and had similar other baseline characteristics.

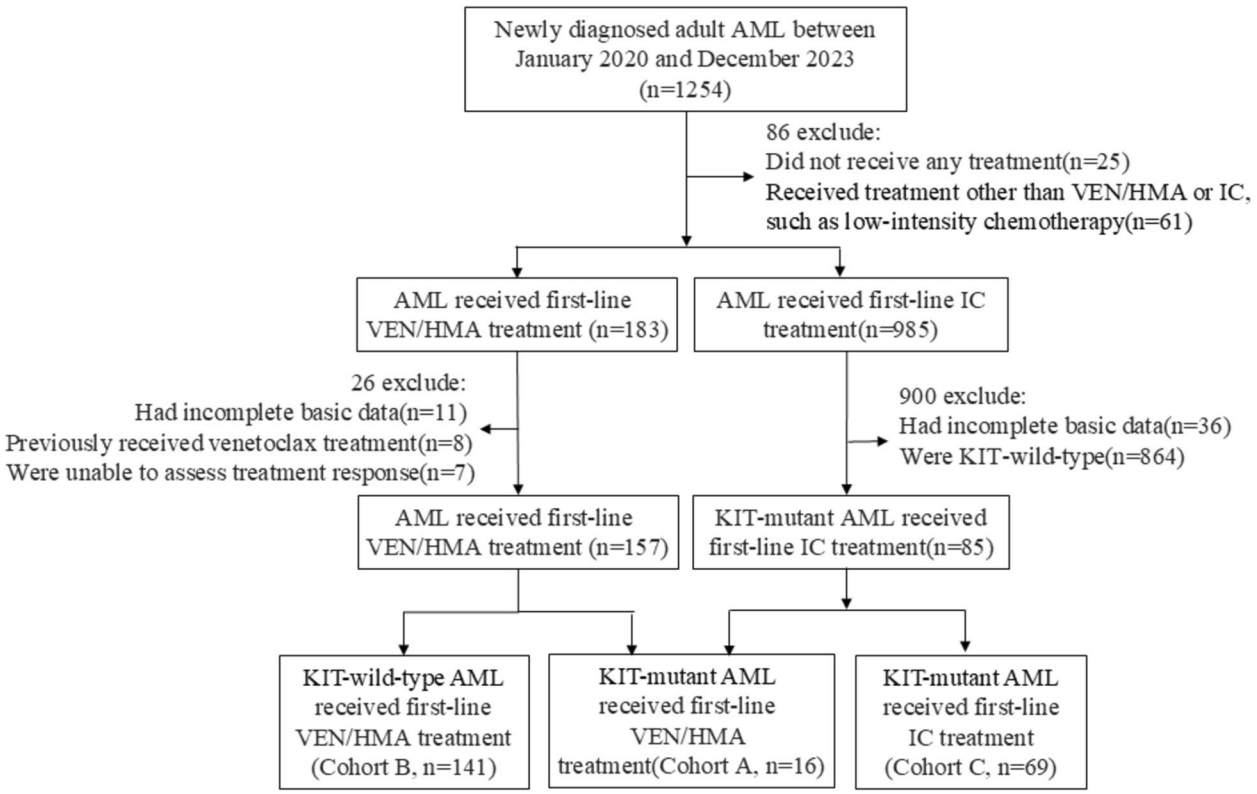

Fig. 1 The flowchart of patient selection. AML: acute myeloid leukemia; VEN: venetoclax; HMA: hypomethylating agent; IC: intensive chemotherapy

Table 1 Baseline characteristics of patients

	KIT mutated treated with VEN/HMA (Cohort A, $n = 16$)	KIT wild-type treated with VEN/HMA (Cohort B, $n = 141$)	p	KIT mutated treated with IC (Cohort C, $n = 69$)	p
Age			0.165		< 0.001
< 65	9 (56.3%)	54 (38.3%)		65 (94.2%)	
≥ 65	7 (43.8%)	87 (61.7%)		4 (5.8%)	
Sex			0.936		0.365
Male	8 (50.0%)	69 (48.9%)		43 (37.7%)	
Female	8 (50.0%)	72 (51.1%)		26 (62.3%)	
ECOG PS			0.015		0.320
< 2	10 (62.5%	45 (31.9%)		54 (78.3%)	
≥ 2	6 (37.5%)	96 (68.1%)		15 (21.7%)	
Type of HMA			0.391		/
Azacitidine	16 (100%)	14 (9.9%)		/	
Decitabine	0 (0%)	127 (90.1%)		/	
Bone marrow blast			0.986		0.576
< 50%	7 (43.8%)	62 (44.0%)		25 (36.2%)	
≥ 50%	9 (56.3%)	79 (56.0%)		44 (63.8%)	
FAB-M5	6 (37.5%)	56 (39.7%)	0.864	23 (33.3%)	0.751
ELN 2022 risk group			< 0.001		0.489
Favorable	14 (87.5%)	38 (27.0%)		62 (89.9%)	
Intermediate	0 (0%)	25 (17.7%)		3 (4.3%)	
Adverse	2 (12.5%)	78 (55.3%)		4 (5.8%)	
CBF-AML	14 (87.5%)	10 (7.1%)	< 0.001	64 (92.8%)	0.854
FLT3-ITD/TKD mutation	4 (25.0%)	31 (22.0%)	1.000	11 (15.9%)	0.622
TP53 mutation	0 (0.0%)	20 (14.2%)	0.226	0 (0.0%)	/
Allo-HSCT	4 (25.0%)	18 (12.8%)	0.339	28 (40.6%)	0.247

ECOG PS: Eastern Cooperative Oncology Group Performance Status; AML: acute myeloid leukemia; CBF: core binding factor; FAB: French, American, and English; VEN: venetoclax; HMA: hypomethylating agents; IC: intensive chemotherapy; ELN: European LeukemiaNet; Allo-HSCT: allogeneic hematopoietic stem cell transplantation

Outcomes of patients with and without KIT mutations receiving VEN/HMA therapy

When receiving first-line VEN/HMA therapy, the ORR of KIT-mutant AML patients was significantly lower than that of KIT-wild-type patients (18.8% vs 72.3%, $p < 0.001$), and the MRD-negative rate was also significantly lower (18.8% vs 68.1%, $p < 0.001$) (Fig. 2A). The 60-day mortality rates of the two cohort were similar (6.4% vs 6.3%, $p = 1.000$). For patients who were primarily resistant to frontline VEN/HMA therapy or relapsed after remission, the ORR of salvage therapy was 90.9% in KIT-mutant AML and 42.6% in KIT wild-type AML, with significant difference ($p = 0.003$). At a median follow-up of 13.1 months in the KIT-mutant cohort and 17 months in the KIT-wild-type cohort, the median EFS of KIT-mutant AML patients was significantly shorter (1.9 months vs 7.8 months, $p < 0.001$; Fig. 2B). There was no significant difference in OS between the two cohorts ($p = 0.502$; Fig. 2C).

In KIT-mutant AML, the prevalence of CBF-AML is significantly higher than in KIT wild-type AML. Consequently, most KIT-mutant AML patients are classified into the ELN 2022 low-risk group. To mitigate confounding effects, we analyzed the outcomes of patients after propensity matching for CBF-AML subtype, ELN 2022 risk stratification and ECOG PS. After PSM, 24 patients were matched by a 1:1 matching ratio, and all the baseline characteristics were similar between the two matched cohorts (Table S1 in Supplementary material). After PSM, KIT-mutant AML showed significantly lower ORR compared to KIT-wild-type AML (25.0% vs. 75.0%, $p = 0.014$, Fig. 2D). MRD-negative rates were also markedly reduced in KIT-mutant CBF-AML (25.0% vs. 75.0%, $p = 0.014$, Fig. 2D). At a median follow-up of 10.9 months in KIT-mutant cohort and 15.2 months in KIT-wild-type cohort, median EFS was significantly shorter in KIT-mutant AML (2.3 months vs. not reached, $p = 0.003$; Fig. 2E). No significant difference in median OS between the two groups ($p = 0.470$, Fig. 2F).

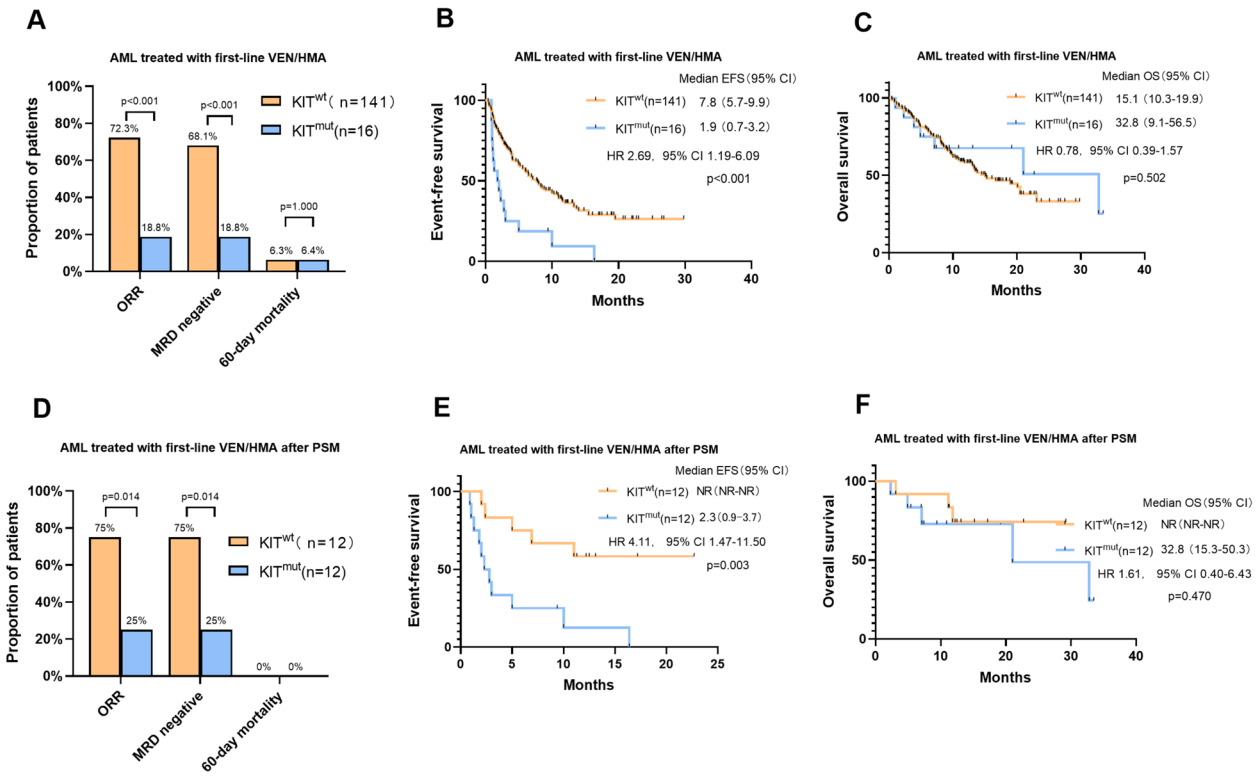

Fig. 2 Outcomes of patients with and without KIT mutations receiving VEN/HMA therapy. **A** Response and early death, **B** EFS and **C** OS in all patients. **D** Response and early death, **E** EFS, and **F** OS in patients after PSM for CBF-AML subtype, ELN 2022 risk stratification and ECOG PS. AML: acute myeloid leukemia; PSM: propensity score matching; KIT^{mut}: KIT mutant; KIT^{wt}: KIT wild-type; VEN: venetoclax; HMA: hypomethylating agent; EFS: event-free survival; OS: overall survival; ORR: overall response rate; MRD: measurable residual disease; NR: not reached; HR: hazard ratios; CI: confidence interval

Outcomes of patients with KIT mutations receiving VEN/HMA or IC

We analyze the efficacy and survival of patients with KIT-mutant AML who received first-line VEN/HMA treatment ($n=16$) or IC ($n=69$). KIT-mutant AML patients treated with IC achieved significantly higher ORR compared to those receiving VEN/HMA (78.3% vs. 18.8%, $p<0.001$). MRD-negative rates were also markedly higher in the IC cohort (75.4% vs. 18.8%, $p<0.001$). No significant difference in early mortality between IC and VEN/HMA cohorts (Fig. 3A). For patients who were primarily resistant to frontline IC therapy or relapsed after remission, the ORR of salvage therapy was 78.6%, which was similar with KIT-mutant patients receiving frontline VEN/HMA therapy($p=0.660$). At a median follow-up of 18.1 months in IC cohort and 13.1 months in VEA/HMA cohort, median EFS was significantly longer in the IC cohort (12.2 months vs. 1.9 months, $p<0.001$; Fig. 3B). No significant difference in median OS was observed between the two treatment groups (Fig. 3C).

However, there were significant age-related differences in patients receiving VEN/HMA or IC therapy, which may introduce potential bias. Thus, we analyzed the outcomes of patients after propensity matching for age. After PSM, 28 patients were matched by a 1:1 matching ratio, and all the baseline characteristics were similar between the two matched cohorts (Table S2 in Supplementary material). Patients treated with VEN/HMA demonstrated significantly lower ORR compared to the IC-treated group (21.4% vs. 71.4%, $p=0.008$) and a concurrent tendency toward reduced MRD-negative rates (21.4% vs.57.1%, $p=0.053$). Both cohorts exhibited 0% 60-day mortality (Fig. 3D). At a median follow-up of 13.1 months in the VEN/HMA cohort and 26.4 months in the IC cohort, the median EFS was significantly shorter in the VEN/HMA cohort (1.3 months vs. 8.7 months, $p=0.021$, Fig. 3E). No statistically significant difference in median OS was observed between the two treatment arms (Fig. 3F).

Multivariate analyses for response and survival

Multivariate logistic regression analyses were conducted to assess the predictive factors for response and Cox regression analyses were conducted to assess

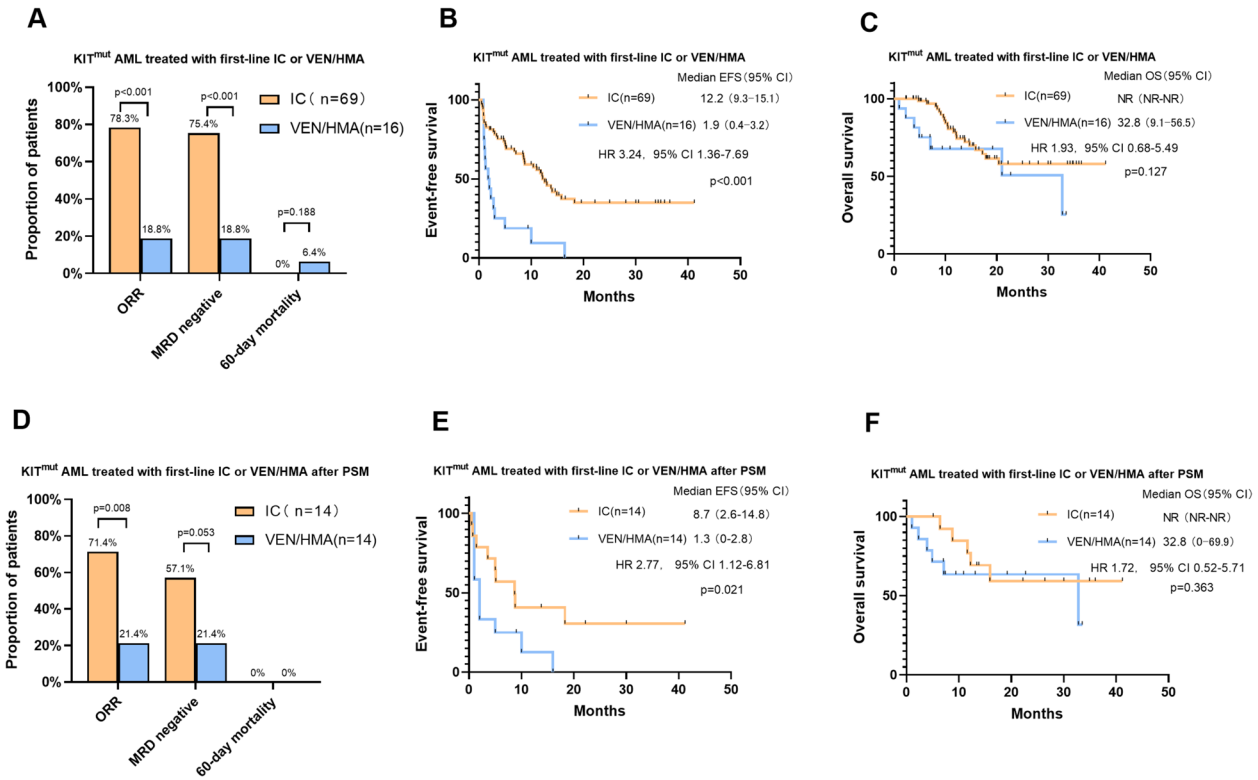

Fig. 3 Outcomes of patients with KIT mutations receiving VEN/HMA or IC. **A** Response and early death, **B** EFS and **C** OS in all patients. **D** Response and early death, **E** EFS, and **F** OS in patients after PSM for age. AML: acute myeloid leukemia; PSM: propensity score matching; KIT^{mut}: KIT mutant; IC: intensive chemotherapy; VEN: venetoclax; HMA: hypomethylating agent; EFS: event-free survival; OS: overall survival; ORR: overall response rate; MRD: measurable residual disease; NR: not reached; HR: hazard ratios; CI: confidence interval

the risk factors for EFS in patient receiving VEN/HMA. The analysis demonstrated that KIT mutations were independently associated with lower ORR (OR 0.020, 95% CI 0.002–0.211, $p = 0.001$) and shorter EFS (HR 6.319, 95% CI 2.659–15.012, $p < 0.001$) in AML patients receiving first-line VEN/HMA therapy (Fig. 4A, B). Other factors significantly linked to reduced ORR including FAB-M5 subtype (OR 0.376, 95% CI 0.159–0.887, $p = 0.026$), ELN intermediate/adverse risk stratification (OR 0.088, 95% CI 0.011–0.728, $p = 0.024$) and TP53 mutations (OR 0.331, 95% CI 0.113–0.973, $p = 0.045$, Fig. 4A). Additional predictor of shorter EFS was FLT3-ITD/TKD mutation (HR 1.650, 95% CI 1.022–2.662, $p = 0.040$, Fig. 4B).

The impact of allo-HSCT as time-dependent covariates on EFS and OS in patients receiving VEN/HMA was analyzed using Mantel–Byar test. Allo-HSCT was identified as a positive predictor for OS ($p = 0.001$, Fig. 5B).

Discussion

To our knowledge, this represents the first cohort study investigating the impact of KIT mutations on outcomes following VEN/HMA therapy in AML. In our study, the presence of KIT mutations was associated with a significantly lower ORR and MRD-negative rate. Moreover, the median EFS was markedly shorter in KIT-mutant patients. These findings suggest that KIT mutations may serve as a predictive marker for poor response and shorter EFS in AML patients treated with VEN/HMA.

The occurrence of KIT mutations is significantly higher in CBF-AML compared to other AML subtypes [10–13], a pattern consistently observed in our cohort. To eliminate potential confounding effects of the CBF-AML genetic background, PSM analysis was conducted. The results demonstrated that KIT mutations were still associated with poor response to VEN/HMA therapy regardless of the CBF-AML subtype. However, the

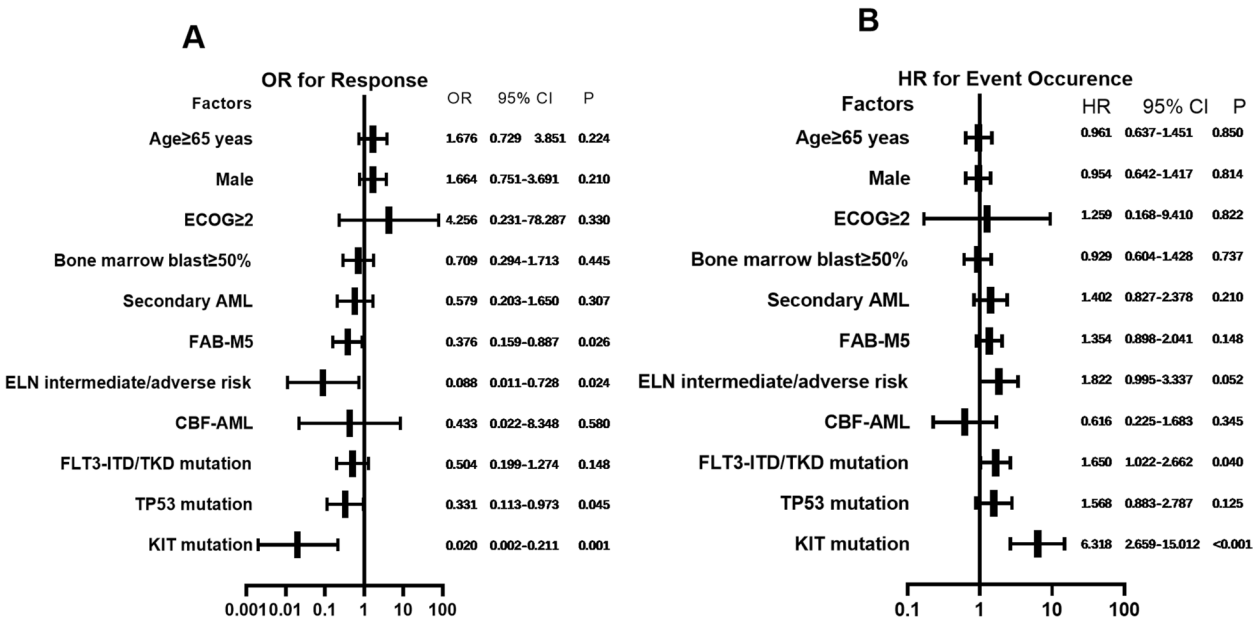

Fig. 4 Predictors for ORR and EFS. **A** Factors associated with ORR. **B** Factors associated with EFS. ECOG PS: Eastern Cooperative Oncology Group Performance Status; AML: acute myeloid leukemia; CBF: core binding factor; FAB: French, American, and English; ELN: European LeukemiaNet; Allo-HSCT: allogeneic hematopoietic stem cell transplantation; ORR: overall response rate; EFS: event-free survival; CI: confidence interval; OR: odds ratio; HR: hazard ratios

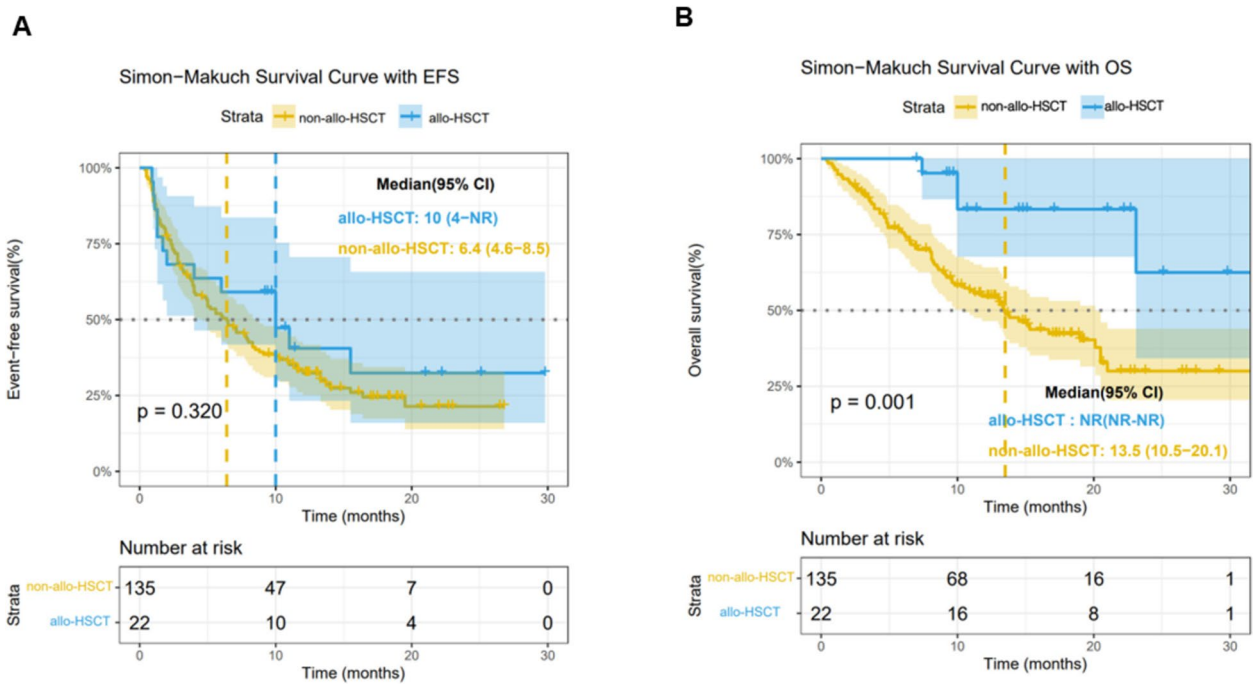

Fig. 5 Simon–Makuch plots of the impact of allo-HSCT on **A** EFS and **B** OS. Allo-HSCT: allogeneic hematopoietic stem cell transplantation; EFS: event-free survival; OS: overall survival; CI: confidence interval; NR, not reached

limited cohort size in our study precluded comprehensive analysis of CBF-AML's prognostic influence, particularly regarding molecular subtyping interactions. We anticipate that future investigations with larger sample sizes or functional laboratory studies will help clarify this issue.

When comparing VEN/HMA therapy to IC in KIT-mutant AML patients, IC demonstrated significantly superior outcomes with respect to ORR, MRD-negative rates and EFS.

KIT-mutant patients with primary resistance to frontline VEN/HMA or those who relapsed post-treatment still exhibited high response rates to second-line salvage therapy, which may be one of the reasons for the non-significant difference in OS. Additionally, allo-HSCT was identified as a positive predictor for OS in patients receiving first-line VEN/HMA treatment. The heterogeneity in post-frontline therapies (e.g., consolidation chemotherapies and allo-HSCT) may variably impact the overall survival of patients.

Multivariate analysis further confirmed KIT mutations as an independent predictor of lower ORR and shorter EFS. Additional factors associated with adverse prognosis in AML receiving VEN/HMA treatment include FAB-M5 subtype, ELN intermediate/high risk, FLT3-ITD/TKD mutations and TP53 mutations, consistent with previous literature reports on molecular determinants of treatment resistance and disease progression [9, 21–23].

The issue of resistance to venetoclax has received widespread attention. Several confirmed mechanisms of drug resistance include dysregulation of BCL-2 family anti-apoptotic protein expression, BCL-2 acquired mutations, p53 inactivation, metabolic changes in the electron transport chain, mitochondrial structural alterations, and resistance mediated by the bone marrow microenvironment [24]. Prior studies demonstrate that shifts in anti-apoptotic dependencies, such as increased expression of BCL-XL, MCL-1, and BCL-w, and/or decreased BCL-2 expression, enable cancer cells to bypass BCL-2 inhibition, driving venetoclax resistance [25–27]. Recent findings reveal that RAS/MAPK activation induces MCL-1 upregulation during venetoclax resistance, which blocks BIM-mediated APOPTOSIS and sustains mitochondrial metabolism and survival, establishing the RAS/MAPK/MCL-1 axis as a critical mechanism of venetoclax resistance in AML [28]. Additionally, activation of the Ras/Raf/MEK/ERK pathway has been reported to transcriptionally upregulate MCL-1, further contributing to venetoclax resistance in AML [22].

The KIT receptor plays a pivotal role in maintaining the self-renewal capacity of hematopoietic stem cells and their differentiation into myeloid and lymphoid lineages by regulating key signaling pathways [29]. Mutations in KIT lead to constitutive activation of its tyrosine kinase domain, which aberrantly transmits downstream signals through PI3 K/AKT pathway, JAK/STAT pathway, MAPK/ERK pathway and Src family kinase pathway [13]. These dysregulated pathways collectively sustain clonal expansion of malignant cells in hematologic malignancies. However, in vivo evidence confirming the role of KIT in mediating venetoclax resistance and its underlying molecular pathways remains lacking. Further studies are warranted to explore these unresolved questions, particularly focusing on potential crosstalk between KIT-driven signaling (e.g., PI3 K/AKT, JAK/STAT, or MAPK cascades) and established resistance mechanisms such as BCL-2 mutations, MCL-1 upregulation via RAS/MAPK activation, or compensatory metabolic adaptations.

Our study has certain limitations that need to be acknowledged. Firstly, the retrospective nature of this study introduced potential selection bias in patient enrollment, and the exclusion of participants with incomplete data further compromised the validity of the research findings. Moreover, again due to the retrospective study design, drug doses were not uniformly regulated, which may have influenced patients'survival outcomes. Secondly, the limited sample size reduces the study's credibility and precludes meaningful analysis of how distinct KIT mutation subtypes or co-mutations influence therapeutic outcomes. Thirdly, due to incomplete retrospective data, we were unable to incorporate quality of life assessments and treatment-related toxicity evaluations to preclude more comprehensive evaluation of the treatment's impact on patients. Lastly, while interpreting the findings, it is important to acknowledge the potential risk of Type I errors due to multiple comparisons conducted in this study. The lack of formal adjustment for multiple testing may increase the likelihood of false-positive associations. Larger, prospective studies are needed to validate our findings and further elucidate the mechanisms underlying the adverse effects of KIT mutations on VEN/HMA therapy. Additionally, future research should explore potential therapeutic strategies to overcome resistance in KIT-mutant AML patients, as well as the interplay between different genetic factors.

Conclusions

In summary, our study suggested KIT mutations are associated with poor response and shorter EFS in AML patients treated with VEN/HMA. These findings have important implications for risk stratification and treatment selection in this patient population.

Abbreviations

allo-HSCT Allogeneic hematopoietic stem cell transplantation

AML	Acute myeloid leukemia
CBF	Core binding factor
CI	Confidence interval
CR	Complete remission
CRi	CR with incomplete recovery of blood counts
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EFS	Event-free survival
ELN	European LeukemiaNet
FAB	French, American, and English
HMA	Hypomethylating agent
HR	Hazard ratio
IC	Intensive chemotherapy
MLFS	Morphologic leukemia-free state
MRD	Measurable residual disease
ORR	Overall response rate
OS	Overall survival
PSM	Propensity score matching
VEN	Venetoclax

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-025-02637-w.

Supplementary Material 1.

Supplementary Material 2.

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Author contributions
D.J. conceived the study; W.S. and Q.Y. wrote the paper; D.H. revised the paper; Y.L. J.L., Q.C., H.D., L.L., B.C. collected data; Y.G. analysed data. All authors reviewed the manuscript.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethical Review Committee of Ningbo Medical Center Lihuili Hospital (approval No. KY2023PJ351). The procedures used in this study adhere to the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects and/or their legal guardian(s).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. DiNardo CD, Pratz KW, Letai A, Jonas BA, Wei AH, Thirman M, et al. Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study. Lancet Oncol. 2018;19(2):216–28.
2. DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med. 2020;383(7):617–29.
3. Pollyea DA, Pratz K, Letai A, Jonas BA, Wei AH, Pullarkat V, et al. Venetoclax with azacitidine or decitabine in patients with newly diagnosed acute myeloid leukemia: long term follow-up from a phase 1b study. Am J Hematol. 2021;96(2):208–17.
4. DiNardo CD, Pratz K, Pullarkat V, Jonas BA, Arellano M, Becker PS, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood. 2019;133(1):7–17.
5. Cherry EM, Abbott D, Amaya M, McMahon C, Schwartz M, Rosser J, et al. Venetoclax and azacitidine compared with induction chemotherapy for newly diagnosed patients with acute myeloid leukemia. Blood Adv. 2021;5(24):5565–73.
6. Maiti A, Qiao W, Sasaki K, Ravandi F, Kadia TM, Jabbour EJ, et al. Venetoclax with decitabine vs intensive chemotherapy in acute myeloid leukemia: a propensity score matched analysis stratified by risk of treatment-related mortality. Am J Hematol. 2021;96(3):282–91.
7. Pollyea DA, DiNardo CD, Arellano ML, Pigneux A, Fiedler W, Konopleva M, et al. Impact of venetoclax and azacitidine in treatment-naive patients with acute myeloid leukemia and IDH1/2 mutations. Clin Cancer Res. 2022;28(13):2753–61.
8. Kuusanmaki H, Leppa AM, Polonen P, Kontro M, Dufva O, Deb D, et al. Phenotype-based drug screening reveals association between venetoclax response and differentiation stage in acute myeloid leukemia. Haematologica. 2020;105(3):708–20.
9. Pei S, Pollyea DA, Gustafson A, Stevens BM, Minhajuddin M, Fu R, et al. Monocytic subclones confer resistance to venetoclax-based therapy in patients with acute myeloid leukemia. Cancer Discov. 2020;10(4):536–51.
10. Cancer Genome Atlas Research Network, Ley TJ, Miller C, Ding L, Raphael BJ, Mungall AJ, et al. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. N Engl J Med. 2013;368(22):2059–74.
11. Qin YZ, Zhu HH, Jiang Q, Jiang H, Zhang LP, Xu LP, et al. Prevalence and prognostic significance of c-KIT mutations in core binding factor acute myeloid leukemia: a comprehensive large-scale study from a single Chinese center. Leuk Res. 2014;38(12):1435–40.
12. Krauth MT, Eder C, Alpermann T, Bacher U, Nadarajah N, Kern W, et al. High number of additional genetic lesions in acute myeloid leukemia with t(8;21)/RUNX1-RUNX1T1: frequency and impact on clinical outcome. Leukemia. 2014;28(7):1449–58.
13. Katagiri S, Chi S, Minami Y, Fukushima K, Shibayama H, Hosono N, et al. Mutated KIT tyrosine kinase as a novel molecular target in acute myeloid leukemia. Int J Mol Sci. 2022;23(9):4694.
14. Padmakumar D, Chandraprabha VR, Gopinath P, Vimala Devi ART, Anitha GRJ, Sreelatha MM, et al. A concise review on the molecular genetics of acute myeloid leukemia. Leuk Res. 2021;111: 106727.
15. Cairoli R, Beghini A, Grillo G, Nadali G, Elice F, Ripamonti CB, et al. Prognostic impact of c-KIT mutations in core binding factor leukemias: an Italian retrospective study. Blood. 2006;107(9):3463–8.
16. Schnittger S, Kohl TM, Haferlach T, Kern W, Hiddemann W, Spiekermann K, et al. KIT-D816 mutations in AML1-ETO-positive AML are associated with impaired event-free and overall survival. Blood. 2006;107(5):1791–9.
17. Ishikawa Y, Kawashima N, Atsuta Y, Sugiura I, Sawa M, Dobashi N, et al. Prospective evaluation of prognostic impact of KIT mutations on acute myeloid leukemia with RUNX1-RUNX1T1 and CBFB-MYH11. Blood Adv. 2020;4(1):66–75.
18. Dohner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345–77.
19. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DA, Gralnick HR, et al. Proposals for the classification of the acute leukaemias: French–American–British (FAB) co-operative group. Br J Haematol. 1976;33(4):451–8.

20. Zhang Z. Propensity score method: a non-parametric technique to reduce model dependence. Ann Transl Med. 2017;5(1):7.
21. DiNardo CD, Tiong IS, Quaglieri A, MacRaild S, Loghavi S, Brown FC, et al. Molecular patterns of response and treatment failure after frontline venetoclax combinations in older patients with AML. Blood. 2020;135(11):791–803.
22. Zhang H, Nakauchi Y, Kohnke T, Stafford M, Bottomly D, Thomas R, et al. Integrated analysis of patient samples identifies biomarkers for venetoclax efficacy and combination strategies in acute myeloid leukemia. Nat Cancer. 2020;1(8):826–39.
23. Jin D, He J, Chen H, Wu W, Han X, Le J, et al. Impact of monocytic differentiation on acute myeloid leukemia patients treated with venetoclax and hypomethylating agents. Cancer Med. 2024;13(14): e7378.
24. Sullivan GP, Flanagan L, Rodrigues DA, Ni Chonghaile T. The path to venetoclax resistance is paved with mutations, metabolism, and more. Sci Transl Med. 2022;14(674): eabo6891.
25. Bodo J, Zhao X, Durkin L, Souers AJ, Phillips DC, Smith MR, et al. Acquired resistance to venetoclax (ABT-199) in t(14;18) positive lymphoma cells. Oncotarget. 2016;7(43):70000–10.
26. Choudhary GS, Al-Harbi S, Mazumder S, Hill BT, Smith MR, Bodo J, et al. MCL-1 and BCL-xL-dependent resistance to the BCL-2 inhibitor ABT-199 can be overcome by preventing PI3K/AKT/mTOR activation in lymphoid malignancies. Cell Death Dis. 2015;6(1): e1593.
27. Guieze R, Liu VM, Rosebrock D, Jourdain AA, Hernandez-Sanchez M, Martinez Zurita A, et al. Mitochondrial reprogramming underlies resistance to BCL-2 inhibition in lymphoid malignancies. Cancer Cell. 2019;36(4):369-84. e13.
28. Zhang Q, Riley-Gillis B, Han L, Jia Y, Lodi A, Zhang H, et al. Activation of RAS/MAPK pathway confers MCL-1 mediated acquired resistance to BCL-2 inhibitor venetoclax in acute myeloid leukemia. Signal Transduct Target Ther. 2022;7(1):51.
29. Bowie MB, Kent DG, Copley MR, Eaves CJ. Steel factor responsiveness regulates the high self-renewal phenotype of fetal hematopoietic stem cells. Blood. 2007;109(11):5043–8.

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